CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS
Volume 24, Number 3, 2009

DOI: 10.1089/cbr.2008.0570

Short Communication

Chronic Lymphocytic Leukemia: Long-Lasting Remission with Combination of Cyclophosphamide, Somatostatin, Bromocriptine, Retinoids, Melatonin, and ACTH

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Abstract

The usual, initial therapy of patients with chronic lymphocytic leukemia (CLL) involves alkylating agents, corticosteroids, purine analogs, and monoclonal antibodies. The combination of these agents may lead to high complete and overall response rates, but all patients inevitably relapse, and median progression-free survival varies between 16 and 48 months. Further, these treatments present the risk of myelosuppression and infection, so that some of the combination regimens require antibiotic, antiviral, and antimycotic prophylaxis during and after their administration. We treated 4 patients with previously untreated progressive stage I Rai CCL, with a combination of cyclophosphamide, somatostatin, bromocriptine, retinoids, melatonin, and ACTH. All the patients had partial remission after 2 months and continued treatment, which was gradually reduced if lymphocyte count fell below 4000/μL. No patients had disease recurrence, and progression-free survival has not yet been reached (125, 121, 73, and 21 months, respectively). Toxicity was absent, and patients underwent the treatment at home, while carrying out their normal activities.

Key words: chronic lymphocytic leukemia, long-lasting remission, cyclophosphamide, somatostatin, melatonin

Introduction

Chronic lymphocytic leukemia (CLL) is the most frequent type of leukemia in the Western world; its prognosis is estimated by clinical staging systems developed by Rai et al. and Binet et al., which define early- (Rai 0, Binet A), intermediate- (Rai I/II, Binet B), and advanced- (Rai III/IV, Binet C) stage disease, with median estimated survival times of >10, 5–7, and 1–3 years, respectively.[1]

Initiation of therapy for early-stage disease does not result in prolonged survival; therefore, therapy is instituted only in patients with intermediate or advanced disease. In the last decade, other treatments, including nucleoside analogs and monoclonal antibodies, have been introduced, in addiction to the traditional approach with alkylanting agents.

The combination of these agents has led to high complete and overall response rates, when administered as initial therapy, but all patients inevitably relapse, and median progression-free survival varies between 16 and 48 months.[2–4] Further, these treatments present the risk of myelosuppression and infection, so that some of the combination regimens require antibiotic, antiviral, and antimycotic prophylaxis during and after their administration. Due to the lack of curative treatment, stem-cell transplantation (SCT) has been increasingly performed; however, autologous SCT does not result in cure, and allogeneic SCT is associated with high

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treatment mortality rates.[5,6] In this situation, new therapeutic options that improve the duration of remission and preserve a good quality of life appear very desirable.

Recently, several new agents have been shown to inhibit lymphatic growth. In particular, those without myelotoxicity, such as somatostatin, have aroused great interest for the possibility of being used with myelosuppressive regimens, without causing a further myelosuppression. This association was first described by Di Bella et al., who used cyclophosphamide together with somatostatin, bromocriptine, retinoids, melatonin (1), and ACTH.[7] In 1998, when we began to use this association, it had already been demonstrated that: (1) Somatostatin receptors are present on the membrane of human lymphocytes and leukemia cells[8]; (2) prolactin is an autocrine factor for a human leukemic cell line[9]; (3) transretinoic acid is effective in promyelocytic leukemia, T-cell lymphoma localized to the skin, and other hematologic malignancies[10]; (4) melatonin inhibits the lymphocyte proliferative response to mitogens[11]; and (5) ACTH suppresses lymphocyte blastogenesis in response to phytohemagglutinin and concanavalin A.[12] These studies, together with the well-known action of cyclophosphamide, provided us with the rationale to employ a combination of cyclophosphamide and somatostatin, bromocriptine, retinoids, melatonin, and ACTH, as had been used in patients with CLL and non-Hodgkin's lymphoma.[13]

Patients and Methods

Four patients (3 women, 1 man; median age, 52; range, 43–60) with previously untreated progressive stage I Rai CLL were treated with cyclophosphamide plus somatostatin, bromocriptine, retinoids, melatonin, and ACTH. Diagnosis of CLL was made in the Department of Hematology; at that time, all the patients were in Rai stage 0, with lymphocytosis in blood and bone marrow only (all having diffuse bone marrow involvement). Patients began our treatment as soon as there was a clear evidence of disease progression, with evolution in Rai stage 1. Median time between initial diagnosis of CLL and the beginning of the treatment was 42.75 (range, 20–64) months. Each patient gave written informed consent prior to study inclusion.

According to the NCI Working Group,[14] complete remission (CR) was requiring normal complete blood cell count (CBC), absence of lymphadenopathy and symptoms, no hepatomegaly, and bone marrow normocellular for age, with less than 30% of nucleated cells being lymphocytes; partial remission (PR) was requiring a $\geq$50% reduction in lymphadenopathy, and/or a $\geq$50% reduction in the size of liver and/or spleen (if abnormal prior to therapy), and/or a 50% improvement over baseline of one or more of the following: platelets, polymorphonuclear leucocytes, or hemoglobin; finally, progressive disease meant a $\geq$50% increase of at least 2 lymph nodes, or appearance of new palpable lymph nodes, or a $\geq$50% increase in the absolute number of lymphocytes, or transformation to a more aggressive histology. Response to treatment was assessed after 2 months by clinical examination, blood count, serum chemistry profile, ultrasound examination, or computed tomography. Patients who responsed continued the treatment for 3 months and more, with monthly blood count determination. Treatment was tapered if lymphocyte count became <4000/μL. Patients were reassessed every 3 months; a bone marrow examination was required if response could be considered a CR one. Toxicity was evaluated by using criteria developed by the World Health Organization.

Treatment regimen

Patients received a combination of cyclophosphamide, somatostatin, bromocriptine, retinoids, melatonin, and ACTH. Cyclophosphamide was given orally at a dose of 100 mg/day (50 mg at 2 p.m. and 50 mg at 9 p.m.). Somatostatin was administered subcutaneously (S.C.) at a dose of 3 mg/day during 8 hours, using a syringe pump. The administration started at least 3 hours after dinner and those patients who were psycologically unable to accept this type of administration received a single s.c. injection of octreotide (1 mg/day) 3 hours after dinner. Bromocriptine was given orally at a dose of 2.5 mg/day (1.25 mg at 2 p.m. and 1.25 mg at 9 p.m.). Retinoids: all-transretinoic acid, vitamin A palmitate, and β-carotene were administered orally, at 8 a.m., in 5 mL of vitamin E, at doses of 5 mg, 5000 IU and 20 mg/day, respectively. Melatonin was given orally at a dose of 20 mg/day (10 mg at 2 p.m. and 10 mg at 9 p.m.). ACTH was administered intermuscularly at a dose of 1 mg/week. All the patients were treated for at least 2 months. At the end of this period, those who responded continued. If lymphocyte count decreased to <4000/μL, treatment was gradually reduced until maintenance therapy (MT), at doses of: cyclophosphamide: 50 mg at 2 p.m. 2–3 times/week; somatostatin: 1 mg s.c. during 8 hours 2–3 times/week; bromocriptine: 1.25 mg/day; all-transretinoic acid, vitamin A palmitate, and β-carotene in 2.5 mL of vitamin E, at doses of 2.5 mg, 2500 IU and 10 mg/day, respectively; melatonin: 14–16 mg/day subdivided into 2 administrations; ACTH: 0.20–0.40 mg/week. MT was reached and continued, if during the dose reduction, and/or after, the lymphocyte count did not increase to >5000/μL.

Results and Discussion

All the patients had a partial response after 2 months. Lymphocyte count became <4000/μL within an average period of 4 months (range, 3–6), the initial average lymphocyte count being 47,000/μL (range, 32,000/μL–77,000/μL). By that time, patients also obtained a normal CBC, the complete remission of lymphadenopathy and of the possible CLL-related symptoms. Since this response could be consistent with a CR (under the further condition that also bone marrow had less than 30% lymphocytes), we required a bone marrow examination, but the patients refused to undergo it. Thus, we decided to consider obtained responses as if they were PRs, and patients continued the treatment. As treatment progressed, none had disease recurrence. MT was reached in a median of 2.5 months (range, 2–3.2) and continued thereafter. Progression-free survival has not yet been reached in any of the patients (125, 121, 73, and 21 months, respectively).

Drug toxicity was absent; drowsiness was observed in 1 patient and required adjustment of the daily schedule of melatonin administration (20 mg/day were subdivided into 3 doses, instead of 2, 1 of which was at bedtime).

Despite the limited number of patients, our study provides evidence that patients with previously untreated progressive

stage I Rai CCL may durably respond to combination therapy with cyclophosphamide, somatostatin, bromocriptine, retinoids, melatonin, and ACTH.

Conclusions

The observation of long-lasting remission and very good tolerance justify further evaluation of this regimen, in an attempt to improve the duration of survival and preserve a good quality of life.

Disclosure Statement

I confirm that no competing financial interests exist.

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